

REMARKS

This submission is in response to the Official Action dated January 30, 2003. Claims 47, 49, 52, 53, 56, and 58 have been amended. Claims 42, 47, 49-50, 52-54, 56-61, 63, and 65 are pending. Claim 42 has been withdrawn by the Examiner from further consideration pursuant to 37 C.F.R. 1.142(b). Reconsideration of the above identified application, in view of the above amendments and the following remarks, is respectfully requested.

Claims 47, 49, 53, 56, and 58 have been amended in matters of formal claim language, *i.e.*, to replace parentheses around sequence identifiers with the phrase "as set forth in SEQ ID NO:X."

Claim 52 has been amended to recite a nucleic acid encoding a PAMP having at least 90% sequence identity to SEQ ID NO:14. This is supported by the specification at page 17, lines 20-24. Claim 54, which depends from claim 52, has been amended to conform with the recitation of claim 52.

Claim 58 has been amended to independent form, and to recite a mutant human PAMP less capable than human PAMP as set forth in SEQ ID NO:14 of interacting with a presenilin protein. This amendment is supported throughout the specification, *e.g.*, at page 45, lines 17-29.

No new matter has been added by way of this amendment. Each objection and rejection set forth in the office action is separately addressed below.

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Serial No. 09/541,094
Response to Office Action dated January 30, 2003

Docket No. 1034/1F812US2
Page 9

Oath / Declaration

The Examiner considers the Declaration defective because it does not refer to the previously filed preliminary amendment.

Applicants respectfully submit that this objection is in error. The Examiner cites MPEP 604.08 as support for the objection. Since, upon information and belief, MPEP 604.08 does not exist, applicants assume that this was typographical error, and that the Examiner intended to cite MPEP 608.04.¹ This section is entitled "New Matter By Preliminary Amendment", and relates to amendments adding *disclosure*. The amendment made with the filing of the specification on March 31, 2000 merely included the priority information in the specification, and did not introduce any new matter. The priority information was, in fact, set forth in the inventors' Declaration filed on November 22, 2000.

Further, there is no requirement by Rule 1.66, 1.67(a), (b), (c), or 1.68 (see 37 C.F.R. revised as of February 2003) that the Declaration must refer to a previously filed preliminary amendment, and Applicants are not aware of any other Rule which sets forth such a requirement. Hence, this objection should be withdrawn.

¹ If, in fact, some other section of the MPEP was intended, the Examiner is respectfully invited to contact the undersigned with the correct citation.

Priority

The Examiner has objected to the applicant's claim for domestic priority under 35 U.S.C. §119(e) contending that the provisional application upon which priority is claimed fails to provide adequate support under 35 U.S.C. §112 for claims 47, 49-50, 52-54, 56-61, 63, and 65 of the instant application. The Examiner alleges that SEQ ID NO: 14 comprises 23 additional amino acid residues which would not have been obvious in light of SEQ ID NO: 2.

The applicants respectfully submit that this objection is in error. Contrary to the Examiner's assertions, SEQ ID NO: 2 in the first provisional application dated April 1, 1999 contained the *entire* sequence of SEQ ID NO:14 in the instant application, as well as an additional 23 "propeptide" amino acid residues. Therefore, the first provisional application provides adequate support for SEQ ID NO: 14 in the instant application, and thus establishes full priority to April 1, 1999.

Moreover, even if the first provisional did not disclose the full sequence of SEQ ID NO:14, the instant application would still be entitled to priority to the second provisional application, filed on December 30, 1999, which contained the same exact amino acid sequence as SEQ ID NO: 14 and using the very same sequence identifier (SEQ ID NO:14). Thus, since the second provisional application fully disclosed the SEQ ID NO: 14 amino acid sequence, the instant

application should be awarded, at the very least, a priority date of December 30, 1999.

Finally, the Examiner has cited no reference that is available on the basis of the priority date of this application.

For the above reasons, reconsideration and withdrawal of the Examiner's objection to the priority claim is respectfully requested.

Objection to the Specification

The Examiner has objected to the disclosure because it contains hyperlinks and other forms of browser-executable codes. With this response, the specification has been amended in accordance with MPEP 608.01.

The Examiner has objected to the specification for failing to properly label previously submitted figures. The specification has been amended to remove these figure citations, as the text in the specification fully describes the relevant subject matter of these figures.

35 U.S.C. § 112, 2nd Paragraph - Indefiniteness

The Examiner has rejected claims 47, 49-50, 52-54, and 56-61 for alleged indefiniteness. Each of the Examiner's rejection under this statute is addressed separately below.

The Examiner has rejected claims 47, 49, 53, 56, and 58, contending that the recitation of the term "PAMP (SEQ ID NO: X)" as used in the claims is unclear and ambiguous. The applicants have amended these claims to recite "PAMP as set forth in SEQ ID NO:X" and now believe the claims to be in allowable form.

The Examiner has rejected claims 52 and 54, contending that the specification fails to define the term "function-conservative variant". In response, the applicants have amended claim 52 so that the claim no longer recites this term. Accordingly, it is believed that this amendment overcomes this rejection and requested that the rejection be withdrawn.

The Examiner has rejected claim 58, contending that the specific limitations of the claim are not clearly set forth. Claim 58 has been rewritten in independent form and per the Examiner's suggestion, thus obviating the basis of the rejection.

Accordingly, in view of the above arguments and amendments, Applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. §112, 1st Paragraph - Written Description

The Examiner has rejected claims 47, 49-50, 52-54, and 56-61 for alleged lack of written description.

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Serial No. 09/541,094
Response to Office Action dated January 30, 2003

Docket No. 1034/1F812US2
Page 13

The Examiner contends that the term "PAMP" as used in claims 47, 49-50, 52-54, and 56-61 can be interpreted to encompass this embodiment as well as active fragments of the protein, naturally occurring variants, and mutant forms of PAMP. The Examiner concludes that the specification does not disclose any other species of "wild type" polynucleotide sequences, which could be considered variants or mutant forms of PAMP.

The applicants respectfully disagree. Claims 47 and 49-50 call for an isolated nucleic acid encoding human PAMP having the specific amino acid sequence set forth in SEQ ID NO:14. Claim 53 recites the specific nucleic acid sequence of SEQ ID NO:13. There can be no question that these claims comply with the written description requirement. The MPEP states (MPEP 2163.II.A.3ii):

Description of a representative number of species does not require the description to be of such specificity that it would provide individual support for each species that the genus embraces. For example, in the molecular biology arts, if an applicant disclosed an amino acid sequence, it would be unnecessary to provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acids encoding a given amino acid sequence, but not necessarily any particular species. Cf. *In re Bell*, 991 F.2d 781, 785, 26 USPQ2d 1529, 1532 (Fed. Cir. 1993) and *In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994).

The remaining claims call for mutants or variants of the human PAMP sequence. Contrary to the Examiner's assertion, the specification describes mutants of human PAMP which are capable of interacting with presenilin. Notably, Example 2 reports the making of no less than 8 mutants of SEQ ID NO:14, having C230A, D336A, Y337A, Δ 312-369, Δ 312-340, D458A, P633A, F635A, S683A, and Δ 630-668 mutations (page 43, line 24 to page 44, line 4). This example also describes the effect these mutations have on PAMP function and A β processing, *e.g.*, with regards to A β 40 and A β 42 secretion, accumulation of C-99 and C83 β APP stubs, the levels of soluble β APP, as well as the capability of binding to presenilin fragments. The skilled artisan, being in possession of the amino acid sequence of these mutants by simple modification of SEQ ID NO:14, could easily derive nucleic acid sequences encoding the same by introducing the corresponding codons encoding the substitute amino acid.

Claims 56 and 59-60 call for an isolated nucleic acid encoding a mutant PAMP having a mutation in an amino acid residue corresponding to one or more specific amino acid residues in SEQ ID NO:14. Human PAMP mutants having mutations in the same specific amino acid residues are described and characterized in Example 2. Accordingly, the subject matter of these claims is adequately described by the specification. Similarly, amended claim 58 calls for an isolated nucleic acid encoding a mutant PAMP being less capable of interacting with a presenilin, and having a deletion corresponding to one of two specific deletions of

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human PAMP, described and characterized in Example 2. These deletion mutants were less capable of interacting with presenilin, as evidenced by the co-precipitation experiments and indicated by the reduced A β secretion.

The Examiner contends that the deletion mutants were "incapable" of interacting with presenilin. However, on page 45, lines 20-22, the specification states (emphasis added):

However, both the PAMP Δ ₃₁₂₋₃₆₉ mutant and the PAMP Δ ₃₁₂₋₃₄₀ deletion mutant significantly reduced the amount of PS1 which could be co-immunoprecipitated with PAMP. Interestingly, the reduction in efficiency of binding to PS1 was proportional to the reduction in A β secretion induced by each deletion mutant.

A reduction in efficiency of binding cannot be proportional to anything if the binding efficiency is zero, *i.e.*, the PAMP deletion variants were wholly incapable of interacting with presenilin. Accordingly, the subject matter of these claims is adequately described by the specification.

As amended, claims 52, 54, 63, and 65 call for an isolated cell comprising a vector encoding a variant of human PAMP having at least 90% sequence identity to SEQ ID NO:14. As described above, the specification describes several mutants or variants. These representative PAMP mutants are within the at least 90% sequence identity range. As reported by the specification, some of the mutations had no observable effect on PAMP function, while others resulted in a decreased (but still present) binding to presenilin (page 44, lines 13-

23; page 45, lines 20-22). Thus, polypeptides or enzymes which have at least 90% amino acid identity to SEQ ID NO:14 as determined by BLAST or FASTA algorithms, and which have a capability to interact with a presenilin can easily be envisioned by the skilled artisan.

Support for naturally occurring variants and mutant forms of PAMP can also be found in the specification at page 10, lines 11-26. The specification states that fragments include, but are not limited to, peptides that contain an epitope, preferably a conserved domain, and specific fragments that interact with PS1 or PS2, or both. The specification also states that PAMP encompasses naturally occurring variants including other mammalian variants, allelic variants from other human sources, and mutant forms including artificial PAMP mutants created by standard techniques such as site directed mutagenesis or chemical synthesis.

Therefore, Applicant's were clearly in possession of the invention defined by the current claims at the time of filing of the application as evidenced by the written description.

35 U.S.C. §112, 1st Paragraph - Enablement

The Examiner has rejected claims 47, 49-50, 52-54, and 56-61 for alleged lack of enablement.

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Serial No. 09/541,094
Response to Office Action dated January 30, 2003

Docket No. 1034/1F812US2
Page 17

It is respectfully submitted that the claims are fully enabled by the specification. Claims 47, 49, and 50 now call for a "human PAMP as set forth in SEQ ID NO: 14," and claim 53 recites the specific nucleotide sequence set forth in SEQ ID NO:13. These claims are clearly enabled.

The remaining claims recite mutant or variant human PAMP. The Examiner asserts as follows (office action, page 14):

With respect to protein variants encoded by the instantly claimed polynucleotide, the specification provides general guidance on alterations which could be made in the human PAMP sequence which would result in a protein with a conserved function. ... With respect to the specific mutants set forth in claims 56, 57, and 58, the specification teaches that the deletion mutants do not bind presenilin, and expression of the other mutants in cells result [in] phenotypic characteristics different than that of wild-type PAMP clearly indicating that the mutants do not have the same properties as wild-type PAMP

It is respectfully submitted that these assertions are incorrect in view of the descriptions provided by the present specification. First, the specification does not only provide general guidance, but also specific guidance on which PAMP mutants are encompassed by the present claims. General guidance on presenilin-binding regions is given, e.g., on page 41, lines 13-19, where it is stated that the PS1/PS2-binding regions of PAMP is in the TM (transmembrane) or C-terminal domain. Specific guidance is given in Example 2, describing working examples of eight PAMP variants. On pages 43 and 44, the structural or putative functional

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properties of each region in which a selected mutation is introduced is provided, and pages 44-46 reports the phenotypic consequences of each structural change (*i.e.*, mutation) after expressing the PAMP variants in cells transfected with a vector encoding the variant PAMP. To summarize, deleting residues 312-340 from the central conserved region of PAMP resulted in a reduction in A β levels, while deleting residues 312-369 resulted in a "massive" reduction (page 44, lines 17-20). These changes were proportional to the reduction in efficiency of the deletion mutants' binding to PS1 (page 45, 22-23). As explained above, differences in A β secretion could *not* be proportional to a difference in presenilin binding if the presenilin binding was zero.

Regarding the other mutants, D336A/Y337A resulted in an increase in A β secretion, while A β secretion of D458A, Δ 630-668, P633A/F635A, and S683A mutants were similar to controls. The results thereby show that these PAMP mutants had at the very least the same, in some instances increased, PAMP function, as compared to wild-type human PAMP. Accordingly, the specification identifies regions and specific mutation sites important for PAMP function, including presenilin binding, and provides working examples of how to prepare the mutant nucleic acids and vectors and cells expressing the mutant or variant PAMP sequences.

Claim 52 calls for variant of human PAMP having at least 90% sequence identity to SEQ ID NO:14, and claim 54 is directed to a method of

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producing such a variant PAMP. Contrary to the Examiner's assertions, preparing and identifying such variants, by sequence alignment as described on page 17, lines 8-24 or other known techniques, and testing them for co-precipitation with a presenilin or functional assays as described in Example 2, is mere routine experimentation. As the Federal Circuit articulated in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-4, 190 USPQ 214, 217-19 (CCPA 1976)):

The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Thus, while claim 52, and claims 54, 63, and 65 which depend from claim 52, may require some routine experimentation, such experimentation would not be undue, and the claims therefore comply with the enablement requirement.

Similarly, claims 56, and 58-60 recite PAMP variants with mutations corresponding to specific mutation sites in SEQ ID NO:14, the making and testing of which is described in Example 2. As explained above, the mutants were tested and found to have adequate PAMP function.

Thus a skilled artisan would not need to perform undue experimentation in making the invention within the scope of the claims. Therefore,

the scope of the claims is commensurate with the enablement provided by the disclosure.

35 U.S.C. §102(b) - Anticipation

The Examiner has rejected claims 47, 49-50, and 52-53 as being anticipated by Genbank Accession Number D87442 ("D87442").

The applicants respectfully traverse this rejection. It is also noted that Genbank D87442 has already been considered in a previous office action (mailed 06/12/02) by the instant Examiner. In the previous office action, the Examiner allowed claims 46-50, which recited SEQ ID NO:14. Nevertheless, to advance prosecution, claims 47, 49, and 50 have been amended to recite specific PAMP sequences "as set forth by SEQ ID NO:14." As previously noted by Applicant and the Examiner during the prosecution of this application, the D87442 reference does not disclose SEQ ID NO:13 or SEQ ID NO: 14. Accordingly, reconsideration and withdrawal of the rejection of claims 47, 49 and 50 is earnestly requested.

Further, as amended, claim 52 recites "[a]n isolated cell transfected with a vector, which vector comprises a nucleic acid encoding a function-conservative variant of human PAMP having at least 90% amino acid identity to SEQ ID NO: 14 and being capable of interacting with a presenilin[.]"

The Examiner has noted on page 21 of the Office Action that the coding sequence was not in frame. Thus, the D87442 vector construct could not encode, and thus

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does not enable, a sequence having 90% sequence identity to SEQ ID NO:14 and being capable of interacting with a presenilin. As set forth by the MPEP (section 2121.02; entitled "Compounds and Compositions -- What constitutes Enabling Prior Art):

When a prior art reference merely discloses the structure of the claimed compound, evidence showing that attempts to prepare that compound were unsuccessful before the date of invention will be adequate to show inoperability. *In re Wiggins*, 488 F.2d 538, 179 USPQ 421 (CCPA 1971).

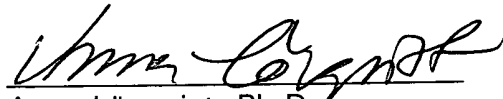
Accordingly, D87442 does not constitute enabling prior art to claims 52 or 53. All of the claims are therefore novel over the D87442 reference, and reconsideration and withdrawal of this rejection is earnestly solicited.

* * *

In view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,



Anna Löqvist, Ph.D.

Limited Recognition Under 37 C.F.R.
10.9(b) (see attached)
Representative for Applicants

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Serial No. 09/541,094
Response to Office Action dated January 30, 2003

Docket No. 1034/1F812US2
Page 23



Marked-Up Specification

Accompanying April 30, 2003 Amendment
For U.S. Serial No. 09/541,094
Docket No. 1034/1F812-US2

Paragraph at page 8, line 21 to page 9, line 6:

Various structural features characterize PAMP (GenBank; Accession No. Q92542; SEQ ID NO: 14). The nucleotide sequence (SEQ ID NO: 13) of human PAMP predicts that the gene encodes a Type 1 transmembrane protein of 709 amino acids (SEQ ID NO:14), the protein having a short hydrophilic C-terminus (~20 residues), a hydrophobic transmembrane domain (15-20 residues), and a longer N-terminal hydrophilic domain which contains several potentially functional sequence motifs as listed below in Table 1. The PAMP sequence also contains a Trp-Asp (WD) repeat (residue 226), at least one "DTG" motif (residues 91 - 93) present in eukaryotic aspartyl proteases, as well as several "DTA/DTAE" motifs (residues 480 - 482, 504 - 506) present in viral aspartyl proteases. There are also four conserved cysteine residues in the Nterminal hydrophilic domain (Cys195, Cys213, Cys230, and Cys248 in human PAMP) having a periodocity of 1617 residues, which may form a functional domain (e.g., a metal binding domain or disulfide bridge for tertiary structure stabilization). Subdomains of PAMP have weak homologies to a variety of peptidases. For example, residues 322 - 343, 361- 405, and 451 - 466 have 46% ($p = 0.03$) similarity to another hypothetical protein; C. elegans aminopeptidase hydrolase precursor signal antigen transmembrane receptor

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zinc glycoprotein (SWISS-PROT; [www.expasy.ch/sprot] World Wide Web (www)
expasy.ch/sprot; Accession No. Q93332).

Paragraph at page 9, line 20 to page 10, line 10:

The invention is further based on the identification of conserved functional domains, based on comparison and evaluation of the predicted amino acid sequences of human (SEQ ID NO: 14), murine (SEQ ID NO: 16), *D. melanogaster* (SEQ ID NO: 18), and *C. elegans* (SEQ ID NO: 12) orthologues of PAMP. "PAMP" can be characterized by the presence of conserved structural features, relative to orthologues from *D. melanogaster* and *C. elegans*. Nucleotide sequences encoding homologous hypothetical proteins exist in mice multiple EST, and *C. elegans* (GenBank; [www.ncbi.nlm.nih.gov] World Wide Web (www) ncbi.nlm.nih.gov; Accession No. Z75714; 37% similarity, $p = 8.7e^{-26}$) (Wilson *et al.*, *Nature* 1994; 368: 32-38). These hypothetical murine and nematode proteins have a similar topology and contain similar functional motifs to human PAMP. The existence of such homology predicts that similar proteins will be detected in other species including *Xenopus*, and Zebra fish, to mention a few such possibilities. By comparing the predicted amino acid sequences of human (SEQ ID NO: 14), murine (SEQ ID NO: 16), *D. melanogaster* (SEQ ID NO: 18), and *C. elegans* (SEQ ID NO: 12) PAMP proteins, we have deduced a series of conserved functional domains.

One domain has chemical similarities to cyclic nucleotide binding domains of other

proteins, and may have some regulatory role on a potential complex formed between PS1:PAMP and the C-terminal fragment of β APP, derived either from a- or b-secretase. These putative functional domains are sites for therapeutic target development by deploying drugs which might interact with these sites to modulate β APP processing via this complex.

Paragraph at page 38, line 24 to page 39, line 8:

The PAMP gene. Chromosomal locations and genetic map positions of the murine and human PAMPS were obtained from public genetic and transcriptional maps [(www.ncbi.nlm.nih.gov)] (World Wide Web (www) ncbi.nlm.nih.gov). The gene encoding PAMP is located on human chromosome 1 near the genetic markers D1S1595 and D1S2844. The 5'- end of the PAMP gene is embedded in the 5'- end of the coatmer gene encoded on the opposite strand. The human PAMP gene is close to a cluster of markers which have yielded positive, but sub-significant evidence for linkage to or association with Alzheimer Disease in two independent genome wide surveys (Kehoe P, *et al.* Hum Mol Genet 1999; 8: 237-245). The murine PAMP maps within a 700 Kb interval of murine chromosome 1 which contains the gene defect associated with *Looptail* phenotype in mice (Underhill DA, *et al.*, Genomics 1999; 55: 185-193). Mice heterozygous for *Looptail* show developmental defects in dorsal axial structures including notochord, brain, spinal cord, and somites (Greene ND, *et al.*, Mech Dev 1998; 73: 59-72.), which are

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reminiscent of those observed in PS1-^{-/-} mice (Shen J, *et al.*, Cell 1997; 89: 629-639; Wong PC, *et al.*, Nature 1997; 387:288-292). These observations suggest that the presenilin: PAMP complex may be involved in both β APP and *Notch* processing.

Paragraph at page 40, line 20 to page 41, line 12:

These results were confirmed in HEK293 cells over-expressing either β APP^{Swedish} or the SpC99- β APP cDNA. The latter encodes the C-terminal 99 residues of β APP (corresponding to the products of β -secretase cleavage) plus the β APP signal peptide. The interaction of PAMP appears much stronger with C99- β APP than that with C83- β APP. However, C83- β APP is much less abundant in these cells [(Fig. 6b, middle panel, lanes 1-4)]. In fact, PAMP does interact with both C99- and C83- β APP stubs [(see Fig. 6c, lane 9 and Fig. 8d)]. Cumulatively, these results indicate that PAMP likely interacts with the C-terminal derivatives of β APP which are the immediate precursors of A β and p3. However, of greater interest, the genotype of the co-expressed PS1 molecule dynamically influenced the interaction between PAMP and C99-/C83- β APP stubs. Thus, more C-terminal β APP fragments co-immunoprecipitated with PAMP in cells expressing the FAD-associated PS1-L392V mutation compared to cells expressing wild type PS1 (and equivalent quantities of nicastrin and C99- β APP). Conversely, much less C-terminal β APP derivatives co-immunoprecipitated with PAMP in cell lines expressing the

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loss-of-function PS1-D385A mutation (despite the presence of very large amounts of C-terminal β APP derivatives in these cells). These effects are more easily seen in cells over-expressing the C99- β APP construct. However, similar but less pronounced differences were also observed in cells over-expressing full-length β APP^{Swedish}. More importantly, the PS1-sequence-related differences in the interaction of PAMP with C-terminal β APP derivatives were most evident within 24 hours of transient transfection of PAMP. By 72 hours, the PS1-sequence-related differences were largely abolished. This dynamic change in the interaction of PAMP with C99/C83- β APP was not due to changes in the levels of PS1, C-terminal β APP derivatives or PAMP. One interpretation of these results is that the presenilins may be dynamically involved in regulating or loading PAMP with the substrates of β -secretase.



**BEFORE THE OFFICE OF ENROLLMENT AND DISCIPLINE
UNITED STATES PATENT AND TRADEMARK OFFICE**

LIMITED RECOGNITION UNDER 37 CFR 10.9(b)

Anna Lovqvist is hereby given limited recognition under 37 CFR 10.9(b) as an employee of the Darby & Darby P.C. law firm to prepare and prosecute patent applications wherein the patent applicant is the client of the Darby & Darby P.C. law firm, and the attorney or agent of record in the applications is a registered practitioner, located in the United States, who is a member of the Darby & Darby P.C. law firm. This limited recognition shall expire on the date appearing below, or when whichever of the following events first occurs prior to the date appearing below: (i) Anna Lovqvist ceases to lawfully reside in the United States, (ii) Anna Lovqvist's employment with the Darby & Darby P.C. law firm ceases or is terminated, or (iii) Anna Lovqvist ceases to remain or reside in the United States on an H1B1 visa.

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Expires: February 4, 2004

Harry I. Moatz

Director of Enrollment and Discipline